

## Unearthing Prehistoric Tumors, and Debate

By George Johnson

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When they excavated a Scythian burial mound in the Russian region of Tuva about 10 years ago, archaeologists literally struck gold. Crouched on the floor of a dark inner chamber were two skeletons, a man and a woman, surrounded by royal garb from 27 centuries ago: headdresses and capes adorned with gold horses, panthers and other sacred beasts.

But for paleopathologists — scholars of ancient disease — the richest treasure was the abundance of tumors that had riddled almost every bone of the man's body. The diagnosis: the oldest known case of metastasizing prostate cancer.

The prostate itself had disintegrated long ago. But malignant cells from the gland had migrated according to a familiar pattern and left identifiable scars. Proteins extracted from the bone tested positive for PSA, prostate specific antigen.

Often thought of as a modern disease, cancer has always been with us. Where scientists disagree is on how much it has been amplified by the sweet and bitter fruits of civilization. Over the decades archaeologists have made about 200 possible cancer sightings dating to prehistoric times. But considering the difficulties of extracting statistics from old bones, is that a little or a lot?

A recent report by two Egyptologists in the journal *Nature Reviews: Cancer* reviewed the literature, concluding that there is "a striking rarity of malignancies" in ancient human remains.

"The rarity of cancer in antiquity suggests that such factors are limited to societies that are affected by modern lifestyle issues such as tobacco use and pollution resulting from industrialization," wrote the authors, A. Rosalie David of the University of Manchester in England and Michael R. Zimmerman of Villanova University in Pennsylvania. Also on the list would be obesity, dietary habits, sexual and reproductive practices, and other factors often altered by civilization.

Across the Internet, news reports made the matter sound unequivocal: "Cancer Is a Man-Made Disease." "Cure for Cancer: Live in Ancient Times." But many medical experts and archaeologists were less impressed.

"There is no reason to think that cancer is a new disease," said Robert A. Weinberg, a cancer researcher at the Whitehead Institute for Biomedical Research in Cambridge, Mass., and the author of the textbook "The Biology of Cancer." "In former times, it was less common because people were struck down in midlife by other things."

Another consideration, he said, is the revolution in medical technology: "We now diagnose many cancers — breast and prostate — that in former times would have remained undetected and been carried to the grave when the person died of other, unrelated causes."

Even with all of that taken into account, there is a fundamental problem with estimating ancient cancer rates. Two hundred suspected cases may not sound like much. But sparsity of evidence is not evidence of sparsity. Tumors can remain hidden inside bones, and those that dig their way outward can cause the

bone to crumble and disappear. For all the efforts of archaeologists, only a fraction of the human bone pile has been picked, with no way to know what lies hidden below.

Anne L. Grauer, president of the Paleopathology Association and an anthropologist at Loyola University of Chicago, estimates that there are roughly 100,000 skeletons in the world's osteological collections, and a vast majority have not been X-rayed or studied with more modern techniques.

According to an analysis by the Population Reference Bureau, the cumulative total of everyone who had lived and died by A.D. 1 was already approaching 50 billion, and had nearly doubled by 1750. (The analysis refutes the oft-made assertion that more people are alive today than have ever lived on earth.) If those figures hold, the number of skeletons in the archaeological database would represent barely one ten-thousandth of 1 percent of the total.

Within that minuscule sample, not all of the remains are complete. "For a long time archaeologists only collected skulls," said Heather J. H. Edgar, curator of human osteology at the Maxwell Museum of Anthropology at the University of New Mexico. "For the most part, there's no way to know what the rest of those people's skeletons might have said about their health."

So how are scientists to evaluate, for example, the significance of the handful of fossilized examples of osteosarcoma, a rare bone cancer that mostly affects young people? (What may be the oldest case was found in 1932 by the anthropologist Louis Leakey in a prehistoric relative of man.) Today the incidence of osteosarcoma among people younger than 20 is about five cases per million per year.

"You would need to screen 10,000 individuals to find a case," said Mel Greaves, a professor of cell biology at the Institute of Cancer Research in England, and the author of "Cancer: The Evolutionary Legacy" (Oxford, 2000). Not enough teenage remains have been scrutinized, he said, to draw a meaningful conclusion.

There is a further complication: more than 99 percent of cancers originate not in bone but in softer organs, which quickly decay. Unless they spread to bone, they will most likely go unrecorded.

Ancient mummies would seem to be an exception. But here, too, the pickings have been slim.

Only on rare occasions can pathologists get their hands on a comparatively recent mummy like Ferrante I of Aragon, king of Naples, who died in 1494. When his body was autopsied five centuries later, adenocarcinoma, which begins in glandular tissues, was found to have spread to the muscles of his small pelvis.

A molecular study revealed a typographical error in a gene that regulates cell division — a G had been flipped to A — which pointed to colorectal cancer. The cause, the authors speculated, might have been gluttonous consumption of red meat.

Over the years hundreds of Egyptian and South American mummies have turned up a few other cases. A rare tumor called a rhabdomyosarcoma was found on the face of a Chilean child who lived sometime between A.D. 300 and 600.

Dr. Zimmerman, co-author of the recent review, discovered a rectal carcinoma in a mummy dated between A.D. 200 and 400, and he confirmed the diagnosis with a microscopic analysis of the tissue — a first, he said, in Egyptian paleopathology.

“The fact remains that there are only a minute number of truly ancient mummies and skeletons that show evidence of cancer,” he said. “We just don’t find anything like the modern incidence of cancer.”

Although average life span was lower in ancient Egypt than it is today, Dr. Zimmerman argues that many individuals, especially the wealthy, lived long enough to get other degenerative diseases. So why not cancer?

Other experts have suggested that most tumors would have been destroyed by the invasive rituals of Egyptian mummification. But in a study published in 1977, Dr. Zimmerman showed it was possible for the evidence to survive.

In one experiment, he took the liver from a modern patient who had succumbed to metastatic colon cancer, dried it out in an oven and then rehydrated it — demonstrating, he said, that “the features of cancer are well preserved by mummification and that mummified tumors are actually better preserved than normal tissue.”

But as with skeletons, the problem remains: Given the small sample size, just how much cancer should scientists expect to see?

To get a rough idea, Tony Waldron, a paleopathologist at University College London, analyzed British mortality reports from 1901 to 1905 — a period late enough to ensure reasonably good records and early enough to avoid skewing the data with, for example, the spike in lung cancer caused in later decades by the popularity of cigarettes.

Taking into account variations in life span and the likelihood that different malignancies will spread to bone, he estimated that in an “archaeological assemblage” one might expect cancer in less than 2 percent of male skeletons and 4 to 7 percent of female skeletons.

Andreas G. Nerlich and colleagues in Munich tried out the prediction on 905 skeletons from two ancient Egyptian necropolises. With the help of X-rays and CT scans they diagnosed five cancers — right in line with Dr. Waldron’s expectations. And as his statistics predicted, 13 cancers were found among 2,547 remains buried in an ossuary in southern Germany between A.D. 1400 and 1800.

For both groups, the authors wrote, malignant tumors “were not significantly fewer than expected” when compared with early-20th-century England. They concluded that “the current rise in tumor frequencies in present populations is much more related to the higher life expectancy than primary environmental or genetic factors.”

With so little to go on, archaeology may never have a definitive answer. “We can say that cancer certainly existed, and probably in somewhat lower frequency than it does today,” said Arthur C. Aufderheide, emeritus professor of pathology at the University of Minnesota and co-author of the Cambridge Encyclopedia of Human Paleopathology. That may be as certain as we ever can be.

As scientists continue to investigate, there may be comfort in knowing that cancer is not entirely civilization’s fault. In the normal course of life a creature’s cells must be constantly dividing — millions of times a second. Sometimes something will go wrong.

“Cancer is an inevitability the moment you create complex multicellular organisms and give the individual cells the license to proliferate,” said Dr. Weinberg of the Whitehead Institute. “It is simply a consequence of increasing entropy, increasing disorder.”

He was not being fatalistic. Over the ages bodies have evolved formidable barriers to keep rebellious cells in line. Quitting smoking, losing weight, eating healthier diets and taking other preventive measures can stave off cancer for decades. Until we die of something else.

“If we lived long enough,” Dr. Weinberg observed, “sooner or later we all would get cancer.”